

Figure 1

Arix. 09/833,243 2 0/2 Craig A. Rosen et al. Atty. Docket: 6832.0018-00

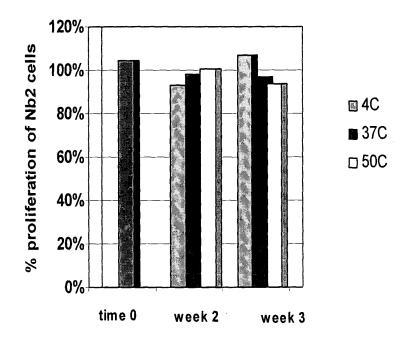


Figure 2

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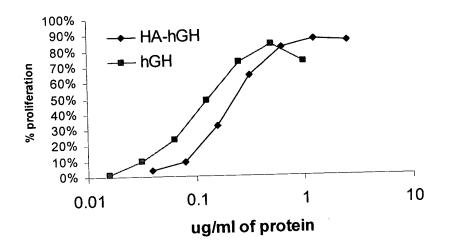


Figure 3A

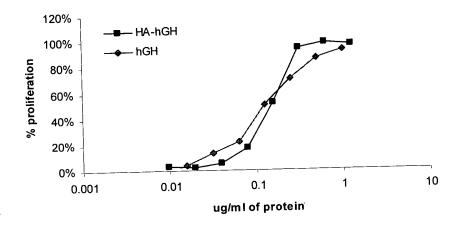


Figure 3B

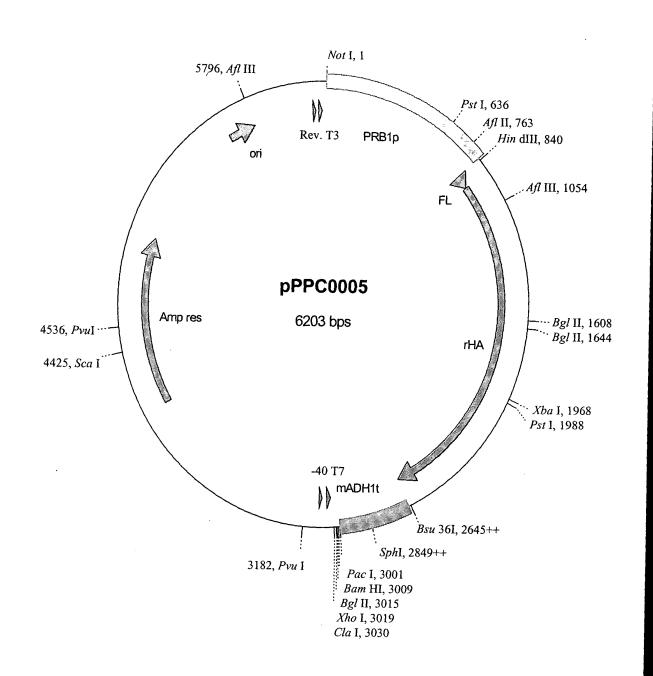


Figure 4

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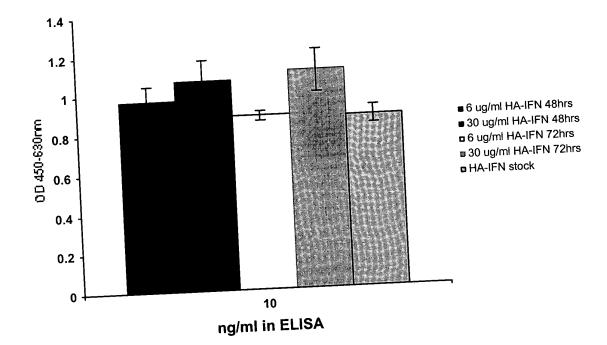
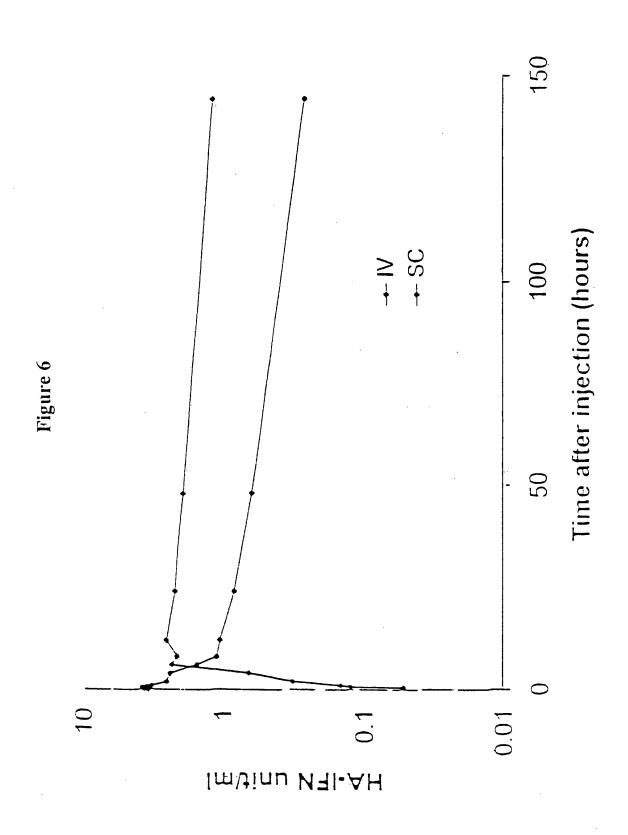
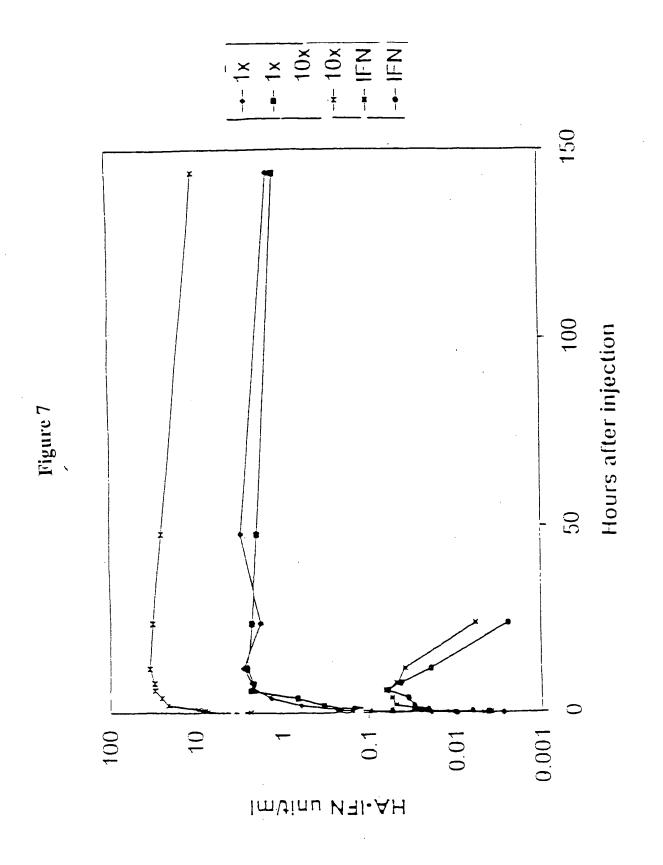
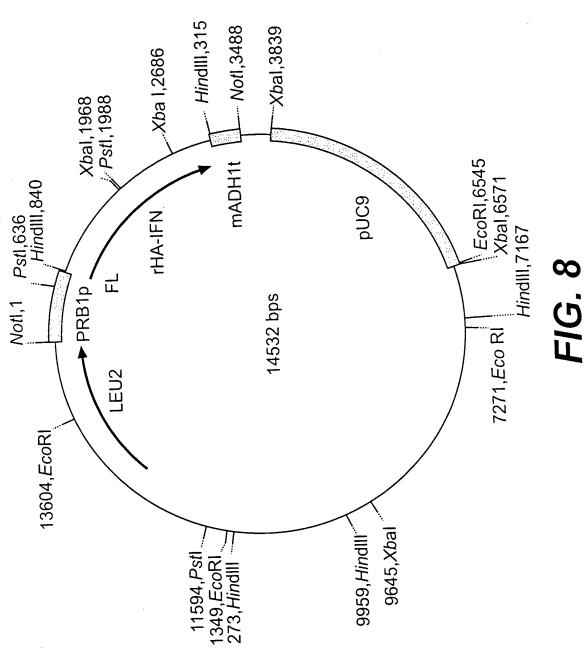


Figure 5





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# Figure 9

1	DAHKSEVAHR HHHHH	FKDLGEENFK HHH HHH	ALVLIAFAQY ННННННННН	LQQCPFEDHV HHHHH	KLVNEVTEFA ННННННННН				
	I			III					
51	KTCVADESAE			RETYGEMADO	CAKOEPERNE				
•	нннн	нннн	ннннн	нннн	н нннн				
101	CFLQHKDDNP HHHH			EETFLKKYLY HHHHHHHHH					
	ıv								
151				KLDELRDEGK НННЕННННН					
					v				
201				VSKLVTDLTK HHHHHHHHHH					
		v	ī	VII	•				
251	<b>LE</b> CADDRADL	AKYIC <b>ENODS</b>	ISSKLKECCE	KPLLEKSHCI	AEVENDEMPA				
	нниннинни	ннннн	нннн	нннннн	Н				
301	DLPSLAADFV HHHH	ESKDVCKNYA HHHHHH	EAKDVFLGMF HHHHHHH	LYEYARRHPD HHHHHH	YSVVLLLRLA HHHHHHHH				
		VIII							
351	KTYETTLEKC		AKVFDEFKPL	VEEPQNLIKQ	NCELFEOLGE				
	нннннннн			ннннннннн	<del></del>				
401	VVEONATIVO	VTKK!/DU!/ct	DTI VEVSENI	GKVGSKCC <b>KH</b>	IX PFAKPMDCAF				
401	ннннннннн		нинининнин		ннннннн				
451	D./.T. O./.T. N.O.T	X	221 my ccm20	XI	T DUDDMUUDU				
451				нининин Нининин	LEVDETYVPK				
		*********		***************************************	•				
501	EFNAETFTFH			ELVKHKPKAT HHH					
		XII							
551	faafvekcc <u>k</u>	<b>ADDKET</b> CFAE	EGKKLVAASQ	AALGL					
	ннннннн	нннн	нниннинни	НН					
•	Loop		Loop						
		4-Asn61 6-Asp89	VII VIII	Glu280-His: Ala362-Glu					
		6-ASP89 2-Glul00	IX	Lys439-Pro					
	IV Gln1	70-Ala176	X	Val462-Lys					
		47-Glu252	XI	Thr478-Pro					
	VI Glu2	66-Glu277	XII	Lys560-Thr	066				

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## Figure 10

### a. Randomisation of Loop IV.

IV

151 APELLFFAKR YKAAFTECC**Q AADKAA**CLLP KLDELRDEGK ASSAKQRLKC HHHHHHHHHH HHHHHHHHHH HHHHHHHHHH

IV

**x** represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

### b. Insertion (or replacement) of Randomised sequence into Loop IV.



ΙV

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.

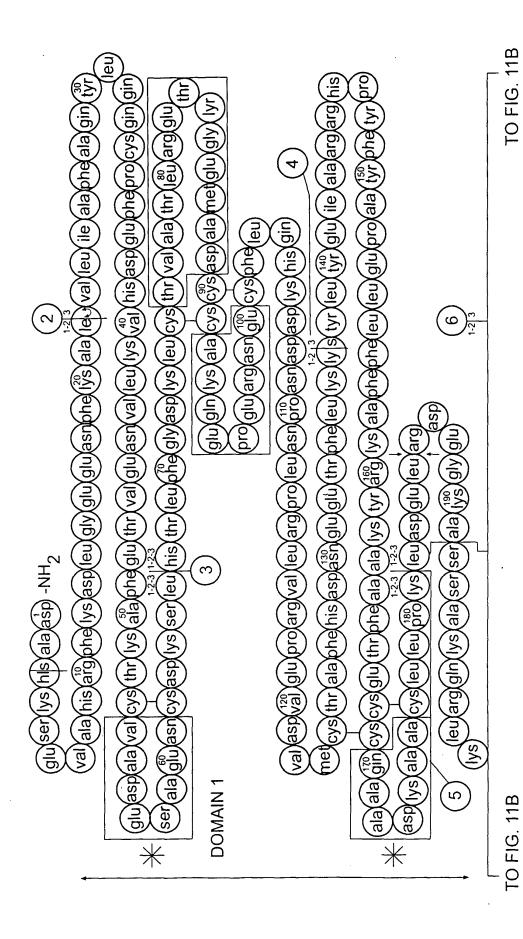


FIG. 11A

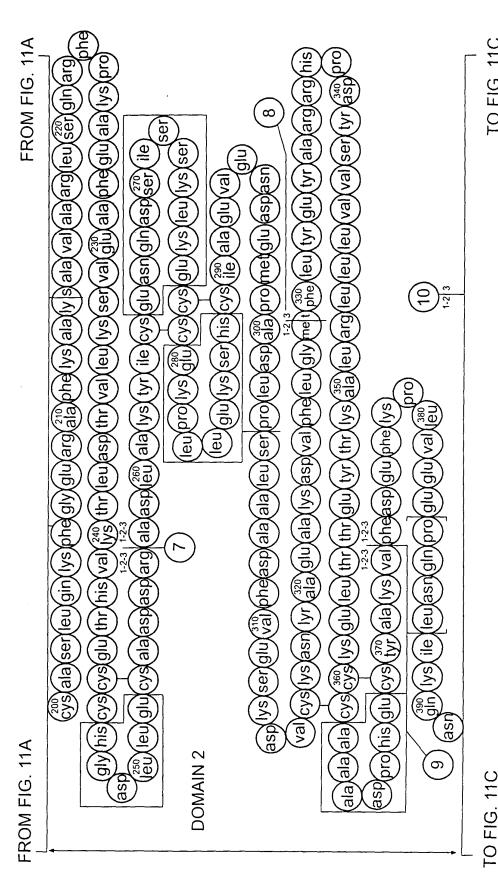


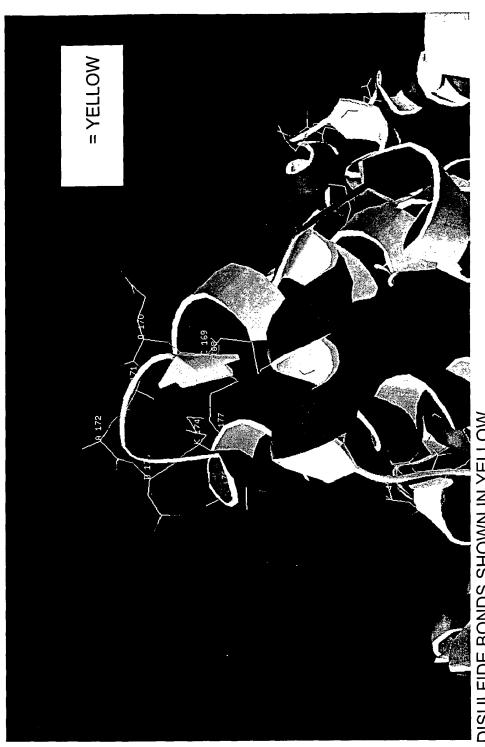
FIG. 11B

TO FIG. 11C

13/20 FROM FIG. 11B aspala)(iys)kyskys)glu)va)phekala)alaphekäspaspme)(va)(ala)(iys)(leu)gin)(glu)(iys)(ffr)(ala)(iys)(pro <sub>Ġlu</sub>∖pro∖tiisXiysҲcysҲtysҲserҲglyXvalXiysXglyXteü\asn\arg\serXvalXglu\xalXeuXthr\pro\tthr\serXvalXgin\pro ʹϲϧ϶ϡʹϯͰͱϯϡͰͼϤϡʹ϶ͼϯϡͼͿϤϡϯϧϧϡʹͼʹͼʹͿϦ϶Ͻϯϧ϶Ͻϯϧ϶Ͻϴ;ͱϯͰϯϠͰ϶ϽͰͼϤϏͼʹͼʹͿϦϴͰϽͰͼϤͿϒ϶ͿͿͰͰ (cysχgluχίευ)pheχgluχginχίευχglyχgluχtyrχlys)pheχgin jasnjal aχίευχιευχναι jargχtyrχthrχlysχlys) lys)arg)metprojcys(ala)diu)asp/tyr/leu)ser)val)val)leu)asn/gin)jeu)cys/val)leu(his)glu)(lys)thr)proj leujser/glu) thr cys(cys(lys) thr val) arg asp ser (asp/ala)tiis)6he(thr)6he(thr)glu)ala)asn)6he(glu)(iys)6ro)val)(tyr)(thr)glu)asp(val)(glu) val/asn/arg/arg/pro/cys/phe/ser/ala/leu HOOC- (%gly)(eu)(ala)(ala)(jin)(ser)(ala) ʹͿͻ϶ʹϏͼͿϥʹͺthrʹͿϲϧ϶ϸͱͱϴʹͼͿͼͿʹϧʹͼͿͼͿʹͿʹͼͿ  $\pm$ FROM FIG. 11B **DOMAIN 3** 

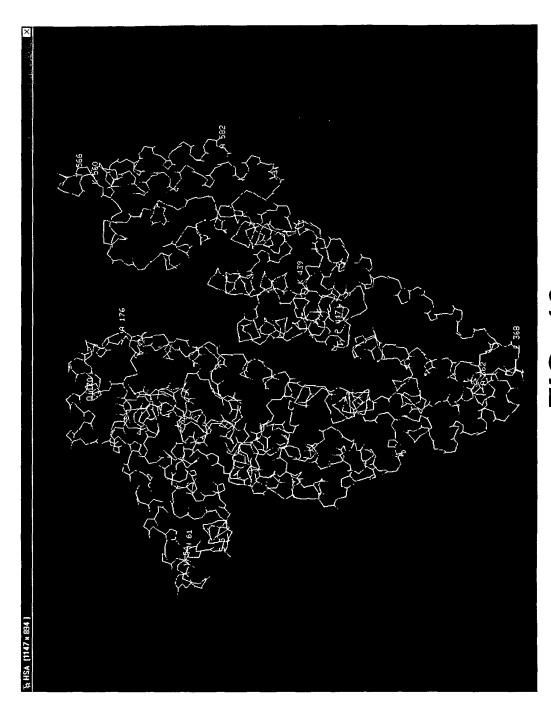
FIG. 11C

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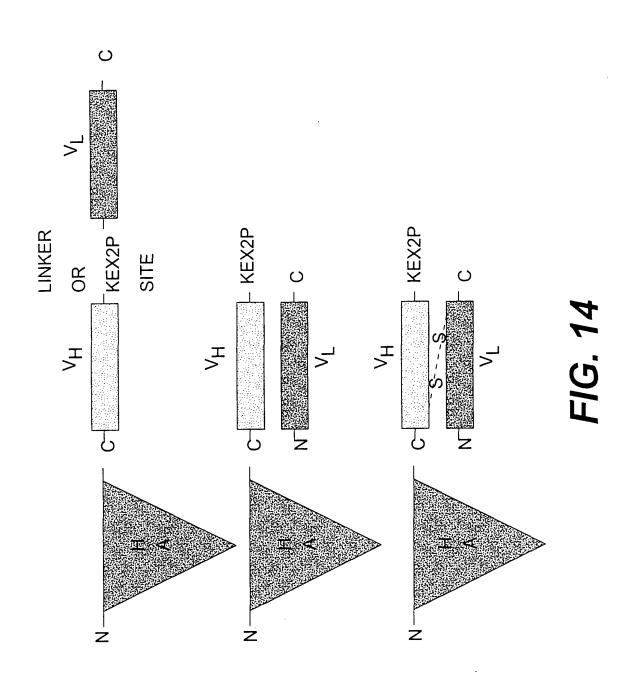


DISULFIDE BONDS SHOWN IN YELLOW

**FIG. 12:** LOOP IV GLU170-A176



# FIG. 13 TERTIARY STRUCTURE OF HA



60 20	120 40	180 60	240	300	360	420 140	480 160
AAA K	GTA V	GAA E	$_{\rm L}^{\cdot}$	GAA E	GTT V	TAT Y	AGG R
TTC F	CAT H	GCT A	ACT T	AAT N	GAG	TTA L	AAA K
AAT N	GAT D	TCA GCT S A	GCA A	AGA R	CCA	TAC Y	GCT A
GAA E	GAA E	GAG E	GTT GCA	GAG AGA E	AGA CCA ( R P	AAA TAC K Y	TTT
GAA E	TGT CCA TTT C	GAT D	ACA T	CT	CGA TTG GTG P R L V F	4AA K	TTC
GGA G	CCA P	GTT GCT O	TTA TGC	CAA GAA Q Q E I	${\rm TTG}_{\rm L}$	TTT TTG A	CTC CTT L
TTG L	TGT C	GTT V	TTA L	CAA Q	CGA R	TTT F	CTC L
GAT D	CAG Q	TGT	AAA K	4AA K	ر درد	ACA I	SAA
AAA K	CAG Q	ACA T	GAC D	GCA A	CTC	GAG E	CCG P
TTT F	$_{\rm L}^{\rm CTT}$	AAA K	GGA GAC	TGT GCA I	AAC N	GAA E	GCC
CGG R	TAT CTT CAG ( Y L Q (	. CA	FTT	. IGC	GAC AAC CCA AAC CTC D N P N L	CAT GAC AAT GAA GAG	TAT GCC CCG (
CAT H	GCT CAG	ACT GAA TTT G	ACC CTT T	GCT GAC 1 A D C	AAC N	GAC D	TAC TTT Y F
GCT A	GCT A	GAA E	ACC T	GCT A	GAC	CAT H	TAC Y
GTT V	TTT E	ACT T	CAT H	ATG M	GAT D	TTT F	CCT
GAG E	GCC	GAA GTA E	TCA CTT S L	GAA E	CAC AAA 0 H K	ACT GCT T A	AGA CAT R
AGT S	ATT I	GAA E	TCA S	TAT GGT C Y G F	CAC	ACT	AGA R
AAG K	$\mathop{\mathrm{TTG}}_{L}$	AAT N	AAA K	TAT Y	CAA Q	TGC C	AGA R
CAC H	GTG V	GTG V	GAC D	ACC	TTC TTG F L	GTG ATG V M	GCC
GCA A	${ m TTG}$	TTA L	TGT C	GAA	TTC F	GTG V	ATT GCC
1 GAT 1 D	GCC A	AAA K	AAT N	CGT R	TGC	GAT	GAA E
7	61	121	181 61	241 81	301	361	421

# Figure 15A

540 180	600	660	720	780 260	840 280	300	960 320
CCA P	TGT C	AGC S		CTT L	AAA CTG AAG GAA TGC TGT GAA K L K E C C E	GCT A	GCT A
TGC CTG TTG CCA C L L P	AGA CTC AAA 7 R L K O	CTG L	ACC	GAC	TGT C	GAG ATG CCT (E M P A	TAT Y
CTG L	CTC L	GCT CGC O	$_{\rm L}^{\rm CTT}$	GCG	76C C	ATG M	AAA AAC ' K N
TGC C	AGA R	GCT A	GAT D	AGG R	GAA E	GAG E	AAA K
GCC	GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAGE LRD EGKA SSAKQ	CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG Q K F G E R A F K A W A V	ACA T	GAC D	AAG K	GAT D	TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC S L A A D F V E S K D V C
GCT A	AAA K	GCA A	GTG V	GAT D	CTG L	AAT N	GTT V
AAA K	GCC A	TGG W	TTA L	GCT A	AAA K	GAA E	GAT D
GAT D	TCT S	GCA A	AAG K	TGT C	AGT S	GTG V	AAG K
GCT A	TCG	AAA K	TCC	GAA E	TCC	GAA E	AGT S
GCT A	GCT A	${ m TTC}$	GTT V	$_{\rm L}^{\rm CTT}$	ATC I	GCC	GAA E
CAA Q	AAG K	GCT A	GAA E	CTG L	TCG S	ATT I	GTT V
TGC	999	AGA R	GCA A	GAT D	GAT D	TGC	TTT F
TGT C	GAA E	GAA E	TTT F	GGA	CAG Q	CAC H	GAT D
GAA E	GAT D	GGA G	GAG E	CAT H	AAT N	TCC	GCT A
ACA T	CGG R	TTT F	GCT A	TGC	GAA E	AAA K	GCT A
TTT F	$_{\rm L}^{\rm CTT}$	AAA K	AAA K	TGC	TGT C	GAA	TTA L
GCT A	GAA E	CAA Q	· CCC P	GAA E	ATC I	TTG	TCA S
GCT A	GAT D	CTC L	TTT F	ACG	TAT Y	CTG	CCT
AAA K	CTC L	AGT S	AGA R	CAC H	AAG K	CCT	TTG L
481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC 161 Y K A A F T E C C Q A A D K A A	AAG CTC GAT G K L D E	GCC AGT CTC C	CAG Q	GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GCT GAT GAC GGG GAC	781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT 261 A K Y I C E N Q D S I S S	841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT 281 K P L L E K S H C I A E V E N D	GAC TTG CCT I D L P S
481 161	541	601 201	661 221	721 241	781 261	841 281	901 301

Figure 15B

1020 340	1080 360	1140 380	1200 400	1260 420	1320 440	1380 460	1440 480
GAT D	TGC C	r AAA CCT CTT 1 K P L 3	GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG V E E P Q N L I K Q N C E L F E Q L G E	. CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT Q N A L L V R Y T K K V P Q V S T	CAT H	TTA L	TCC S
CCT P	AAG K	CCT P	GGA G	TCA S	A A A A	CAG Q	GAG E
AGG CAT R H	TAC TCT GTC GTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG Y S V V L L L R L A K T Y E T T L E K	AAA K	CTT L	GTG V	TGT	AAC	ACA T
AGG R	CTA L	TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT C A A A D P H E C Y A K V F D E F	CAG Q	CAA Q	TGT C	CTG L	TGC
TAT GCA AGA I Y A R I	ACT	GAA E	GAG E	CCC	AAA K	GTC V	TGC
GCA A	ACC T	GAT D	TTT F	GTA V	AGC	GTG V	AAA K
TAT Y	GAA E	TTC	CTT L	AAA K		TCC S	ACA T
SAA E	TAT Y	GTG V	GAG E	AAG K	GTG V	CTA L	GTC V
TTG TAT	ACA T	AAA K	TGT C	ACC	AAA K	TAT Y	AGA R
$_{ m L}^{ m TTG}$	AAG K	GCC	AAC	TAC Y	GGA G	GAC D	GAC
TT	GCC A	TAT Y	CAA Q	CGT R	CTA L	GAA E	AGT S
ATG M	CTT	TGC	AAA K	GTT V	AAC N	GCA A	GTA V
CTG GGC ATG T	AGA R	GAA	ATC	TTA L	AGA R	TGT C	CCA P
CTG L	CTG L	CAT H	TTA L	CTA L	TCA S	CCC P	ACG T
rtc	CTG	CCT	AAT N	CCG	GTC V	ATG M	AAA K
GAT GTC D V I	CTG L	GAT D	CAG Q	AAT N	GAG E	AGA R	GAG E
GAT D	GTG V	GCA A	CCT P	CAG Q	GTA V	AAA K	CAT H
AAG K	GTC V	GCT A	GAG E	TTC	CTT	GCA A	${\rm TTG}_{\rm L}$
GCA A	TCT S	GCC	GAA E	AAA K	ACT T	GAA E	GTG V
GAG GCA AAG C E A K I			GTG V	TAC AAA TTC C Y K F Ç	CCA P	CCT	TGT C
961 321	1021 341	1081 361	1141 381	1201	1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 421 P T L V E V S R N L G K V G S K C C K H	1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 441 P E A K R M P C A E D Y L S V V L N Q L	1381 TGT GTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAAA TGC TGC ACA GAG TCC 461 C V L H E K T P V S D R V T K C C T E S

Figure 15C

1500 500	1560 520	ACA 1620 T. 540	1680 560	1740 580	
AAA K	GAG E	ACA T	AAG K	CAA.	
CCC P	AAG K	GCA A	TGC	AGT S	
GTT V	GAG E	AAG K	TGC	GCA A	
TAC GTT CCC Y V P	TCT	G CCC AAG GCA A	AAG TGC 7 K C C	GAC GAT AAG GAG ACC TGC TTT GCC GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA D D K E T C F A E E G K K L V A A S Q	
ACA T	$_{\rm L}^{\rm crr}$	X A	GAG E	GTT V	01
GAA E	GAA ACA TTC AT CCAT GCA GAT ATA TGC ACA CTT E T F T F H A D I C T L	CAA ATC AAG AAA CAA ACT GCA CTT GTG AAA CAC Q I K K Q T A L V E L V K H	GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG	CTT L	1782 585
GAT D	TGC C	AAA K	TTT F	AAA K	CAG
GTC V	ATA I	GTG V	GCT A	AAA K	TCT
GAA E	GAT D	CII	GCA A	GGT	GCA
$_{ m L}^{ m CTG}$	GCA A	GAG E	TTC	GAG E	AAA
TTT TCA GCT CTG GAA GTC F S A L E V	CAT H	GTT V	GAT D	GAG E	CTA CAT TTA AAA
TCA S	${ m TTC}$	CTT	GAT D	GCC	CAT
TTT F	ACC T	GCA	ATG M	TTT F	CTA
7GC	TTC	ACT T	GTT V	TGC C	CAT
CGA CCA R	ACA T	CAA Q	GCT A	ACC T	C TTA TAA CAT C L *
CGA R	GAA E	AAA K	AAA K	GAG E	TTA L
AGG R	GCT A	AAG K	CTG L	AAG K	GGC G
AAC N	AAT N	ATC	CAA	GAT D	TTA L
GTG V	TTT F	CAA Q	GAG	GAC	GCC TTA GGC A L G
$_{ m L}^{ m TTG}$	GAG TTT AAT GCT E F N A	AGA R	AAA K	GCT A	GCT A
1441 TTG GTG AAC 481 L V N	1501	1561 AGA (	1621 AAA 0 541 K	1681	1741

Figure 15D